The Ethics of Placebo-Controlled Trials

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Declaration of Helsinki

- “In any medical study, every patient--including those of a control group, if any-should be assured of the best proven diagnostic and therapeutic method”

Arguments Against Placebo-Controlled Trials

- Providers should always act in the best interest of the patient.
- There is no circumstance in which an effective treatment should be withheld
- Placebo-controlled trials are unnecessary--they test only significant differences from placebo, not improvement over baseline

(Rothman & Michels, NEJM, 1994,331,394-398)

Ethical Principles

- Respect for patient autonomy
  - Patient must be informed and choose without coercion
- Beneficence
  - Provider should look out for the best interest of the patient
  - The potential benefit to the patient supercedes investigators scientific interests

Why Placebo Controlled Trials are Ethical

- Informed consent
  - Participants must be informed about the rationale for the trial and must understand that they may be assigned to a placebo condition
  - Participants must be informed of any risks of the interventions and the risks associated with delaying treatment if assigned to a placebo condition

Alternative Designs

- Active-Control Equivalence Trials (Noninferiority Trials) (ACET)
- Patients assigned to new treatment or to another treatment believed to be effective
- A null result suggests that the new treatment works because it is not inferior to a known intervention.

Problems with ACET Designs

- Sample size requirements-- violates the principle that trials should be as small as possible
- The meaning of a retained null hypothesis
- No incentive to run a clean trial
  - The poorer the trial, the more error variance and the higher the probability of a null result

How Do You Know If Comparison is Effective?

- FDA data suggest that one third to one half of modern antidepressant trials do not distinguish a known effective drug from a placebo (Temple and Ellenberg, 2000)
- Same for
  - Analgesics, anxiolytics, antihypertensives, hypnotics, antianginal agents, ACE inhibitors, Beta blockers…….

How about Meta-Analysis?

- If meta analysis shows effect for drug, can it be used as the for ACET comparisons?
  - Even if meta analysis shows overall effect, many component studies may have been null
  - No assurance that active treatment would have exceeded placebo in your trial

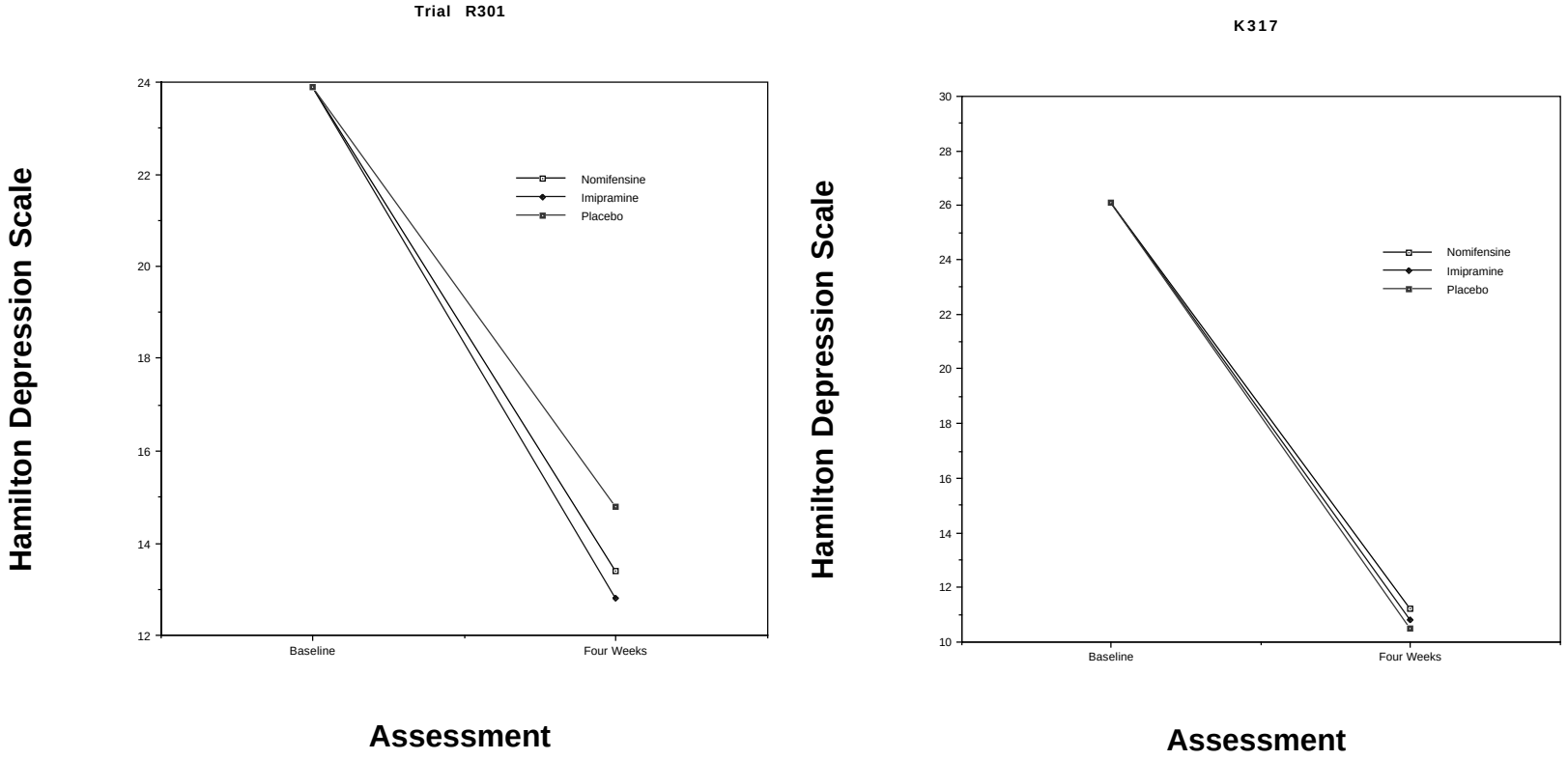
Advantages of 3 groups designs

- Two thirds get active treatment
- Allows comparison for natural history
- If we can not be confident that we can distinguish active treatment from placebo, we can not be sure we can distinguish an effective treatment from a less effective treatment.

Other Solutions

- Early escape trials
  - Valuable for some drug studies
  - May be less valuable for studies on behavior change
- Statistical Approaches
  - Bayesian (Simon, 1999)
  - Prior distribution of effectiveness taken from meta analysis and used for evaluation in ACET trials

Example Comparisons of Nomifensine, Imipramine and Placebo (FDA data)



Summary

- Many interpret Declaration of Helsinki as meaning that placebo controlled trials are unethical
- ACET trials are the best alternative
- ACET trials have significant limitations
- On a scientific level, there are few alternatives to Placebo-Controlled trials